

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 004979.00053	FOR FURTHER ACTION	See item 4 below
International application No. PCT/US2006/035196	International filing date (<i>day/month/year</i>) 08 September 2006 (08.09.2006)	Priority date (<i>day/month/year</i>) 12 September 2005 (12.09.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PRESIDENT AND FELLOWS OF HARVARD COLLEGE		

1.	This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 <i>bis</i> .1(a).																								
2.	This REPORT consists of a total of 5 sheets, including this cover sheet. In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.																								
3.	<p>This report contains indications relating to the following items:</p> <table style="width: 100%;"> <tr> <td style="width: 10%; text-align: center;"><input checked="" type="checkbox"/></td> <td style="width: 30%;">Box No. I</td> <td style="width: 60%;">Basis of the report</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. II</td> <td>Priority</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. III</td> <td>Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. IV</td> <td>Lack of unity of invention</td> </tr> <tr> <td style="text-align: center;"><input checked="" type="checkbox"/></td> <td>Box No. V</td> <td>Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VI</td> <td>Certain documents cited</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VII</td> <td>Certain defects in the international application</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td>Box No. VIII</td> <td>Certain observations on the international application</td> </tr> </table>	<input checked="" type="checkbox"/>	Box No. I	Basis of the report	<input type="checkbox"/>	Box No. II	Priority	<input type="checkbox"/>	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability	<input type="checkbox"/>	Box No. IV	Lack of unity of invention	<input checked="" type="checkbox"/>	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement	<input type="checkbox"/>	Box No. VI	Certain documents cited	<input type="checkbox"/>	Box No. VII	Certain defects in the international application	<input type="checkbox"/>	Box No. VIII	Certain observations on the international application
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4.	The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).																								

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Date of issuance of this report 18 March 2008 (18.03.2008)
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Ernest V. Linek
Banner & Witcoff, Ltd.
28 State Street - 28th Floor
Boston, Massachusetts 02109

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

03 AUG 2007

Applicant's or agent's file reference
004979.00053

FOR FURTHER ACTION

See paragraph 2 below

International application No.
PCT/US 06/35196

International filing date (day/month/year)
08 September 2006 (08.09.2006)

Priority date (day/month/year)
12 September 2005 (12.09.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - C07K 14/81 (2007.01)
USPC - 435/219

Applicant President and Fellows of Harvard College

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US
Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-3201

Date of completion of this opinion
28 March 2007 (28.03.2007)

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US 06/35196

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

- a. type of material

- ☐ a sequence listing
☐ table(s) related to the sequence listing

- b. format of material

- ☐ on paper
☐ in electronic form

- c. time of filing/furnishing

- ☐ contained in the international application as filed
☐ filed together with the international application in electronic form
☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.

PCT/US 06/35196

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-3, 7-10, 14-16, 21, 23	YES
	Claims	1, 4-6, 11-13, 17-20, 22	NO
Inventive step (IS)	Claims	2-3, 7-10, 21, 23	YES
	Claims	1, 4-6, 11-20, 22	NO
Industrial applicability (IA)	Claims	1-23	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1, 4-6, 11-13, 17-20, and 22 lack novelty under PCT Article 33(2) as being anticipated by US 6,214,862 B1 (Fenteany et. al.), herein after Fenteany.

Regarding claim 1, Fenteany teaches the compound of claim 1 (col 2, In 43 to col 3, In 23). Using Fenteany's notation, present claim 1 teaches a structure where X1 = O, Z1 = NH, Z2= CH₂CH₂CH₂Cl, Z3=NH, X2 = O, and A1 = CH₂CHOHCH(CH₃)₂. Fenteany teaches that X1 can be O, Z1 can be NH, Z2 can be CHR where R1 is a C1-C6 haloalkyl (Here R1 would be a C2 Chloroalkyl). Fenteany teaches that Z3 can be NH; X2 = O, and A1 can be (CH)₂(CHOH)(CH)(CH₃)₂.

Regarding claim 4, Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, In 23).

Regarding claim 5, claim 4 teaches a structure equivalent to claim 1 except that Z3 is N-CH(CH₃)PMP, rather than NH. Fenteany teaches that Z3 can be a NR group. Additionally, Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, In 23).

Regarding claim 6, it teaches a structure similar to claim 5 except that Z2 is CH₂CH₂CHOH. Fenteany teaches that Z2 can be a C2-6 hydroxyl (in this case, this would be a C3hydroxyl) and Fenteany teaches a pharmaceutically acceptable carrier or diluent (col 3, In 23).

Regarding claim 11, Fenteany teaches that compositions of the form of compound 3 can inhibit proteasome function in cells (Fenteany col 8, In 38-49).

Regarding claim 12, Fenteany teaches these compositions can function in mammals (col 59, In 1-24).

Regarding claim 13, Fenteany teaches these compositions can treat inflammation (col 58, In 15-18).

Regarding claim 17, Fenteany also teaches this structure. The analysis is similar to that done for claim 1. Here, the only difference from the claim 1 analysis is that Z2 is composed of R4 and R5, where R4 is a halo-lower alkyl group and R5 is either hydrogen or a lower alkyl group. Fenteany teaches that R4 can be a halo-lower alkyl group (col 2, In 64). The present claim R3 and R2 group encompasses hydrogen, which is the same as the teaching of Fenteany, and the R1 group can be the same group previously considered in claim 1.

Regarding claim 18, the claimed R1 group is a side group off of group A1, taught by Fenteany. Fenteany teaches that his A group can encompass these cyclo groups (col. 3 lines 2-23).

Regarding claim 19, the claimed R1 group is a side group off of group A1, taught by Fenteany. Fenteany teaches that his A group can encompass straight chain hydrocarbons of this length (col. 3 lines 2-23).

Regarding claim 20, the claimed R2 group is equivalent to a R group off of Fenteany's Z1 group. Fenteany teaches that Z1 can be NR where this R (equivalent to the claimed R2 group), can be a C1-6 alkyl, which encompasses the structures (methyl, ethyl, etc.) taught by present claim 20.

Regarding claim 22, R4 is equivalent to an R side group off of Fenteany's Z2 group. Fenteany teaches that Z2 can be CHR1 where R1 is a C1-6 haloalkyl, which encompasses the chloro, bromo or iodo ethyl, propyl, isopropyl etc. groups taught by present claim 22.

Claims 14-16 lack an inventive step under PCT article 33(3) as being obvious over Fenteany in view of Goldberg, "Not just research tools - proteasome inhibitors offer therapeutic promise" (hereafter Goldberg).

Regarding claim 14, Fenteany discloses that compounds such as compound 3 are effective at treating medical disorders, but fails to disclose ischemic or reperfusion injury. Goldberg discloses these uses (Goldberg page 340, col 1, para 2).

-----See Supplement Box-----

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Citations and Explanation

Regarding claim 15, it would have been obvious to one of skill in the art that ischemia is a result of vascular occlusion.

Regarding claim 16, Goldberg discloses treating strokes (Goldberg page 340, col 1, para 2).

Claims 2 and 3 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the methods of synthesis of claims 2 and 3.

Claims 7-10, 21, and 23 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach the claimed structures.

Claims 1-23 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.